Critical Reviews in Toxicology, 37:5–10, 2007

ISSN: 1040-8444 print / 1547-6898 online
DOI: 10.1080/10408440601123396

informa
healthcare

Integrating Basic Research on Thyroid Hormone Action into Screening and Testing Programs for Thyroid Disruptors

Shirlee W. Tan
Office of Science Coordination and Policy, U.S. Environmental Protection Agency, Washington, DC, USA; and Smithsonian Institution's National Zoological Park, Washington, DC, USA

R. Thomas Zoeller
Biology Department, Morrill Science Center, University of Massachusetts–Amherst, Amherst, Massachusetts, USA

Thyroid hormone signaling is highly conserved among all the vertebrates, and appears to be present in some invertebrates. Both the components that comprise the system and its general role in development and physiology are evolutionarily conserved, although specific events regulated by thyroid hormones, such as amphibian metamorphosis, may differ among taxonomic groups. The articles in this issue review the thyroid systems of mammals (specifically humans and rodents), fish, amphibians, and birds, and the states of the assays and endpoints used to detect disruption of the thyroid system within a toxicological paradigm. It must be noted that while reptiles represent an enormously important group, they were excluded because there was not enough information in the literature on thyroid toxicology in reptiles at the time that this series of reviews was drafted. Each review highlights the best assays for current regulatory use and those that may be considered for development for future use and research. However, it is important to remember that thyroid research is moving ahead at a fast pace. New thyroid research will impact the design of future thyroid assays used for the detection of thyroid system disruption in ways that may not be anticipated at the time of this writing. Several new areas of exploration are discussed that reveal potential sites of disruption in the thyroid system, including (1) the importance of the neural drive for TSH upregulation, (2) thyroid hormone transport, including cellular transporters like monocarboxylate anion transporter 8 (MCT8) that can regulate thyroid hormone action at the cellular level, and thyroid hormone-binding proteins in the serum that have been shown to differentially bind to environmental chemicals (e.g., certain PCB congeners), and (3) the deiodinases as a target for disruption of thyroid hormone activity in the peripheral thyroid system. The review papers in this issue represent the current state of thyroid assays and endpoints for detection of chemicals that disrupt the thyroid system.

Keywords Deiodinase, Hormone Transport, Iodothyronine, Monocarboxylate Anion Transporter 8 (MCT8), Thyroid Hormones (TH), Thyroid-Stimulating Hormone (TSH), Thyroxin (T_4), 3,3′,5′- triiodothyronine (T_3),

Thyroid hormones (TH) are evolutionarily ancient iodinated molecules, present in all extant vertebrates and in the deuterostome invertebrates (Heyland and Moroz, 2005). Signaling pathways regulated by these hormones affect elements of development, energy balance, and metabolism in all taxonomic groups in which they are found. For example, TH affect metamorphosis in the sand dollar (Heyland et al., 2004), in flounder (Yamano et al., 1994), and in frogs (Buchholz et al., 2005), and are essential for development in birds (McNabb, 2006), and mammals (Zoeller and Rovet, 2004). The hormonally active iodothyronine, 3,3′,5′-triiodothyronine (T_3) is chemically identical in all vertebrates, derived from a precursor (thyroglobulin) conserved among the vertebrates (Novinec et al., 2006), which is iodinated by a similarly conserved peroxidase enzyme system (Taurog, 1999), carried through the blood by conserved binding

Address correspondence to Shirlee W. Tan, Office of Science Coordination and Policy, U.S. Environmental Protection Agency, Washington DC, 20460, USA. E-mail: tan.shirlee@epa.gov, or to R. Thomas Zoeller, Biology Department, Morrill Science Center, University of Massachusetts–Amherst, Amherst, MA 01003, USA. E-mail: tzoeller@bio.umass.edu

proteins (Ekins et al., 1994; Power et al., 2000; Schreiber, 2002), and its actions are mediated by conserved nuclear receptors (Bertrand et al., 2004). The compilation of reviews in this volume demonstrates two important conclusions. First, the chemistry of thyroid hormones, of the proteins (and genes encoding them) involved in thyroid hormone synthesis, and of the ensuing signaling pathways is highly conserved across all vertebrate taxa. Second, thyroid hormone is essential for normal development and for adult health in all vertebrate classes.

Given the importance of thyroid hormone for normal development and physiological function in all vertebrates, it is reasonable to be concerned that environmental factors could influence thyroid function and/or thyroid hormone signaling to the extent that populations would be affected (Brucker-Davis, 1998). In addition, because of the highly conserved nature of TH synthesis, signaling, and regulation, environmental factors that affect thyroid function or TH signaling in one species may well affect thyroid function or TH signaling in another—including in humans. Although one cannot extrapolate thyroid toxicity data directly from one taxonomic group to another, the conservation of regulatory and molecular mechanisms that govern thyroid signaling across vertebrate species allows us to predict effects in untested species, and provides us with sentinel models for both wildlife and human health. There is precedence for environmental chemicals influencing thyroid function in humans with adverse public health consequences (Gaitan, 1989). Environmental effects on the human thyroid gland are well known, in part because of the association of clinical disease with the visible manifestation of goiter (Gaitan, 1989). Goiter, an enlarged thyroid gland, can occur as a result of low dietary iodide, and in populations characterized by endemic goiter, cretinism follows (Delange, 2000, 2001). However, the presence of chemicals in the diet that affect thyroid function can also cause endemic goiter and cretinism (Delange, 1989). The thyroid hormone thyroxin (T_4), in the form of levothyroxine and synthroid, was listed as one of the most commonly prescribed drugs in the United States in the year 2005 by RxList, demonstrating the high incidence of thyroid illness. In addition, thyroid diseases such as hyper- and hypothyroidism are abundant in domestic pets in the United States (Padgett, 2002; Panciera, 2001). Causes of these illnesses are not well characterized, but research is starting to focus more on environmental links to thyroid disease. Similarly, wildlife disease associated with abnormal thyroid function is also being explored as a contributing factor to an animal's susceptibility to other stressors. It is well known that amphibian metamorphosis is one of the most vulnerable times in a frog's life, and this time period is highly dependent on thyroid hormone to progress through normal development from tadpole to frog (Tata, 2006). As a result much research is directed towards understanding the link between thyroid toxicants and amphibian health. The decline in amphibian species across the globe may provide some opportunities to explore how the thyroid system, disease, contaminants, and other stressors may interact (Mendelson et al., 2006).

Considering this, it is important to identify potential thyroid toxicants before wildlife and human populations are exposed to them, especially if they are lipophilic and accumulate through the food chain. In all animals, the ability of the thyroid gland to meet its demands for thyroid hormone is dependent on the availability of iodine and on the function of enzymes involved in TH biosynthesis (Braverman and Utiger, 2004), and these functions are regulated by a complex neuroendocrine system, which integrates information about metabolism and hormone levels (Ahima et al., 2006; Fliers et al., 2006; Lechan and Fekete, 2006). The complexity of thyroid physiology and endocrinology is important for toxicologists as they consider the design of assays to identify potential thyroid toxicants as well as to evaluate the consequences of thyroid toxicants in wildlife and human populations. At the time of this writing, a large number of chemicals are known to affect circulating levels of thyroid hormone by interfering directly with thyroid function (e.g., by inhibiting iodide uptake, thyroperoxidase, or thyroglobulin metabolism) (Brucker-Davis, 1998), with thyroid hormone metabolism (e.g., inducers of glucuronidase enzymes) (Liu et al., 1995), and by interfering directly with thyroid hormone receptors (Zoeller, 2005). Thus, it is essential that screens and tests for thyroid toxicants include measures of thyroid function (i.e., serum hormone levels). However, as new information about thyroid endocrinology becomes available, it will be important to incorporate these new insights into the assays for thyroid toxicants (e.g., adapting assays with endpoints that provide functional measures of thyroid toxicity), and into the interpretation of results from thyroid assays, field observations, and clinical results. Epidemiologists studying the relationship between environmental exposures, thyroid function, and endpoints of adverse effects should also consider the complexity of the thyroid system as well as the diversity of mechanisms by which chemicals can interfere with thyroid signaling. Therefore, the goal of this series of manuscripts is to provide a comprehensive review of thyroid physiology and endocrinology in mammals, fish, amphibians, and birds, and to review existing assays employed to identify thyroid toxicants within the context of this comprehensive review of the basic biology of thyroid hormone.

Several recent papers have revealed new insights into how the thyroid system functions both centrally and peripherally. Here we highlight much of the most recent work that has implications for future thyroid assays. Although this series of documents represents the current state of thyroid assays and endpoints, it is our hope that it will also serve as a framework on which new information can be assimilated into strategies for identifying and characterizing new, and new categories of, thyroid toxicants.

The first paper in this series is designed to provide a thorough background of information about the basic biology of the hypothalamic-pituitary-thyroid (HPT) axis from a toxicological perspective. The HPT axis represents a classic neuroendocrine axis in which specific neurons in the hypothalamus secrete a releasing factor [the tripeptide TRH, which stands for thyrotropin (also known as thyroid-stimulating hormone, or TSH) releasing hormone] into the vasculature that bathes the pituitary gland. In response to TRH, the pituitary gland releases

TSH, which binds to a membrane receptor on the thyroid gland, stimulating the production and release of thyroid hormones.

Thyroid hormones are maintained within a fairly narrow range, in part by the negative feedback action of thyroid hormones on the hypothalamus and pituitary gland. An important set of recent papers documents that, in humans, individual variance in serum T_4 and TSH is far narrower than the population variance (Andersen et al., 2002, 2003). Moreover, the set point around which thyroid hormones are narrowly regulated in humans is predominantly controlled by genetics (Hansen et al., 2004). Specifically, serum T_4 and TSH iare highly correlated among monozygotic twins—in fact, to a significantly greater extent than among dizygotic twins. Considering the narrow range with which serum thyroid hormones are maintained in an individual, these data indicate that differences between individuals leading to the broad population variance are genetically based. In other words, a genetic factor may exist that regulates how much thyroid hormones vary in an individual under normal circumstances. What this genetic factor is and where it functions are yet unknown, but are clearly tied to the hypothalamic and negative feedback control of the HPT axis.

A very prescient hypothesis proposed by Greer et al. (1993) was that an important role of hypothalamic TRH is to control the set-point around which negative feedback operates. This hypothesis is consistent with a recent study using genetic strains of mice that lack either TRH, or the thyroid hormone receptor that mediates negative feedback (TRβ), or both. This study shows that the hypothalamus is the driving influence increasing serum TSH when negative feedback no longer exists (Nikrodhanond et al., 2006). This means that the neural drive to the HPT axis is more potent than the negative feedback effect of thyroid hormone; thus, there may be situations [e.g., caloric restriction (van Haasteren et al., 1996) or infection (Lechan and Fekete, 2004)] that are stimulated (or simulated) by various toxicants, profoundly affecting the HPT axis by affecting neural inputs into the hypothalamus.

Although the HPT axis has been well studied in humans and in other mammalian and nonmammalian vertebrates, new information continues to arise that clearly challenges our understanding of this important neuroendocrine system. For example, a recent paper by Blount and colleagues (Blount et al., 2006) reports that urinary perchlorate is strongly associated with lower serum T4 and higher serum TSH in the a general population of women sampled over the course of 2001–2002, but not in men. This observation challenges our understanding of several very important issues. First, if this observation is confirmed in follow-up studies, it indicates that the human thyroid gland is much more sensitive to perchlorate than previously believed (Greer et al., 2002). Because perchlorate is known to act as a competitive inhibitor of iodide uptake at the sodium/iodide symporter (NIS) (Wolff, 1998), this also challenges our current understanding of the relationship between iodide uptake inhibition and the production of thyroid hormone. Finally, these observations indicate a very significant sex difference in sensitivity of the thyroid gland to perchlorate, an issue that was not well appreciated previously. Thus, as new information continues to arise, we must revise our thinking of the HPT axis and adapt screens and tests to accommodate these new insights.

Another important new area of thyroid research is that of the identification of selective transporters for thyroid hormones. Early work demonstrated that the uptake of ^{125}I-T_4 was tissue dependent (Oppenheimer, 1983), indicating that thyroid hormone is selectively transported into tissues and cells. However, T_4 uptake did not reach a limit of saturation in initial experiments to determine how cellular uptake is regulated, which led to confusion about the potential role of selective transporters in regulating cellular concentrations of T_4 and T_3 (Bernal, 2006). The recent observation that mutations in the human monocarboxylate anion transporter 8 (MCT8) are associated with a form of X-linked mental retardation, severe neurological impairment, and a unique profile of thyroid hormones in serum (Dumitrescu et al., 2004; Friesema et al., 2004) indicate that MCT8 is a selective transporter for T_3 that influences T_3 uptake into neurons. This interpretation is supported by recent in vitro work demonstrating that MCT8 controls the rate-limiting step in cellular T_3 uptake (Friesema et al., 2006).

The recognition that selective transporters control thyroid hormone entrance into tissues indicates that a potentially important site of thyroid disruption is cellular uptake. MCT8-deficient mice recapitulate the unique profile of serum thyroid hormones observed in humans with a mutant MCT8 (Dumitrescu et al., 2006). Thus, one might propose that chemicals interfering selectively with MCT8 transport of thyroid hormones may produce the same kind of unique hormonal profile. However, thyroid hormone transport is a characteristic of several families of membrane proteins, including the sodium-dependent organic anion transporters, the sodium-independent organic anion transport proteins, the heterodimeric amino acid transporters, and the MCTs (Friesema et al., 2005). Thus, it is possible that exogenous compounds that influence MCT8-mediated transport of thyroid hormones may also influence the activity of other transporters and the transport of other chemicals via the MCT8 transporter. Because these transporters exhibit a complex tissue distribution, it is possible that single compounds may produce complex effects on the ability of T_4 and/or T_3 to gain access into specific tissues, and mixtures of compounds may produce even more complex effects. Thyroid hormone transport will be an important potential site of thyroid disruption to explore, and considering that several types of compounds have been shown to bind with high affinity to T_4- and T_3-binding proteins, it is a plausible mechanism. For example, specific polychlorinated biphenyl (PCB) congeners and PCB metabolites are known to bind with high affinity to the T_4-binding protein transthyretin (Darnerud et al., 1996; Cheek et al., 1999; Chauhan et al., 2000; Kato et al., 2004; Marchesini et al., 2006). Thus, there are chemicals known to be structurally similar enough to T_4 to bind to selective binding proteins. The same may be true for thyroid hormone transport. The consequences of transporter

interference will depend on the transporter and the selectivity of interference. The MCT8-deficient mouse exhibits thyrotoxicity in the liver, but hypothyroidism in the brain (Dumitrescu et al., 2006), indicating that interference with a single transporter can produce heterogeneous effects on thyroid hormone signaling. Studies in thyroid toxicology will likely recruit this kind of information when designing new experiments in this exciting new area.

Recent studies have demonstrated that thyroid hormone action can be regulated by dietary components in specific tissues without affecting circulating levels of thyroid hormone. Specifically, Watanabe et al. (2006) found that the bile acid, cholic acid, could prevent body weight gain in mice fed a high-fat diet. Cholic acid binds to the G-protein coupled receptor TGR5 on brown adipocytes, increasing intracellular cAMP and activating the type 2 iodothyronine deiodinase (D2). The action of D2 is to increase the conversion of T_4 to T_3 (St Germain and Galton, 1997). Thus, these investigators have found that a chemical delivered to animals through the diet can selectively alter thyroid hormone action in fat tissue by increasing the metabolic activation of thyroid hormone, *but without changing circulating levels of thyroid hormone*. Considering that there are three types of deiodinases (D1, D2, and D3) with different tissue distributions and different enzymatic activities, it is important to consider that chemicals structurally unrelated to thyroid hormones may have a profound effect on thyroid hormone signaling in some tissues.

In birds, fish, and amphibians, the deiodinases D2 and D3 are universally present. The deiodinase D1 has not been detected in amphibians, lungfish, and agnathans to date. It has been suggested that alternative splicing may dictate which deiodinase is expressed in certain tissues, thus defining developmental changes in thyroid hormone tissue levels (Sutija et al., 2006) and perhaps even responses to chemical exposures.

Although thyroid hormone chemistry and mechanisms of signaling are conserved among vertebrates, the developmental and physiological events controlled by thyroid hormone are different among the vertebrates. Therefore, the first two papers in this series focus on the basic biology of thyroid endocrinology and thyroid toxicology in mammals—mainly in humans and in rodents. An important concept developed during the research for these papers was that the profile of changes in the HPT axis induced by a toxicant appears to depend on the mode of action by which the toxicant interferes with thyroid function. This concept was developed into a separate paper that is the last paper in this series. Subsequent papers focus on the basic biology and toxicology of the thyroid in fish, amphibians (anurans), and birds.

Thyroid endocrinology is undergoing a rapid expansion based on new information and new technologies. Our ability to clearly identify effects of thyroid toxicants and their health consequences—both in an experimental, wildlife population, and in a public health setting—will be dependent on our ability to integrate information from new mechanistic research into toxicological research. Translating basic thyroid endocrinology and toxicology into epidemiological or clinical settings will remain a challenge inasmuch as endpoints of thyroid hormone action in tissues have not been widely developed for collection in a noninvasive manner.

ACKNOWLEDGMENTS

The authors acknowledge Vincent Brown for his invaluable help in editing and formatting the chapter. Support for this document was provided through U.S. EPA contract 68W-01-023.

REFERENCES

Ahima, R.S., Qi, Y., and Singhal, N.S. (2006). Chapter 9: Adipokines that link obesity and diabetes to the hypothalamus. *Prog. Brain Res.* **153**:155–174.

Andersen, S., Pedersen, K.M., Bruun, N.H., and Laurberg, P. (2002). Narrow individual variations in serum T(4) and T(3) in normal subjects: A clue to the understanding of subclinical thyroid disease. *J. Clin. Endocrinol. Metab.* **87**:1068–1072.

Andersen, S., Bruun, N.H., Pedersen, K.M., and Laurberg, P. (2003). Biologic variation is important for interpretation of thyroid function tests. *Thyroid.* **13**:1069–1078.

Bernal, J. (2006). Role of monocarboxylate anion transporter 8 (MCT8) in thyroid hormone transport: Answers from mice. *Endocrinologist.* **147**:4034–4035.

Bertrand, S., Brunet, F.G., Escriva, H., Parmentier, G., Laudet, V., and Robinson-Rechavi, M. (2004). Evolutionary genomics of nuclear receptors: From twenty-five ancestral genes to derived endocrine systems. *Mol. Biol. Evolut.* **21**:1923–1937.

Blount, B.C., Pirkle, J.L, Osterloh, J.D., Valentin-Blasini, L., and Caldwell, K.C. (2006). Urinary percholorate and thyroid hormone levels in adolescent and adult men and women living in the United States. *Environ. Health Perspect.* online: doi:10.1289/ehp.9466 available via http://dx.doi.org.

Braverman, L.E., and Utiger, R.D. (eds.). (2004). *Ingbar's the Thyroid: A Fundamental and Clinical Text*, 9th ed. Lippincott-Raven, Philadelphia.

Brucker-Davis, F. (1998). Effects of environmental synthetic chemicals on thyroid function. *Thyroid.* **8**:827–856.

Buchholz, D.R., Paul, B.D., and Shi, Y.B. (2005). Gene-specific changes in promoter occupancy by thyroid hormone receptor during frog metamorphosis. Implications for developmental gene regulation. *J. Biol. Chem.* **280**:41222–41228.

Chauhan, K.R., Kodavanti, P.R., and McKinney, J.D. (2000). Assessing the role of ortho-substitution on polychlorinated biphenyl binding to transthyretin, a thyroxine transport protein. *Toxicol. Appl. Pharmacol.* **162**:10–21.

Cheek, A.O., Kow, K., Chen, J., and McLachlan, J.A. (1999). Potential mechanisms of thyroid disruption in humans: interaction of organochlorine compounds with thyroid receptor, transthyretin, and thyroid-binding globulin. *Environ. Health Perspect.* **107**:273–278.

Darnerud, P.O., Morse, D., Klasson-Wehler, E., and Brouwer, A. (1996). Binding of a 3,3′,4,4′-tetrachlorobiphenyl (CB-77) metabolite to fetal transthyretin and effects on fetal thyroid hormone levels in mice. *Toxicologist.* **106**:105–114.

Delange, F. (1989). Cassava and the thyroid. In: Environmental Goitrogenesis, E. Gaitan, ed., pp. 173–194. CRC Press, Boca Raton, FL.

Delange, F. (2000). Endemic cretinism. In: *The Thyroid: A Fundamental and Clinical Text*, 8th ed., L.E. Braverman and R.D. Utiger, eds., pp. 743–754. Lippincott Williams & Wilkins, Philadelphia.

Delange, F. (2001). Iodine deficiency as a cause of brain damage. *Postgrad. Med. J.* **77**:217–220.

Dumitrescu, A.M., Liao, X.H., Best, T.B., Brockmann, K., and Refetoff, S. (2004). A novel syndrome combining thyroid and neurological abnormalities is associated with mutations in a monocarboxylate transporter gene. *Am. J. Hum. Genet.* **74**:168–175.

Dumitrescu, A.M., Liao, X.H., Weiss, R.E., Millen, K., and Refetoff, S. (2006). Tissue specific thyroid hormone deprivation and excess in Mct8 deficient mice. *Endocrinologist* **147**(9):4036–4043.

Ekins, R.P., Sinha, A.K., Pickard, M.R., Evans, I.M., and al Yatama, F. (1994). Transport of thyroid hormones to target tissues. *Acta. Med. Austr.* **21**:26–34.

Fliers, E., Alkemade, A., Wiersinga, W.M., and Swaab, D.F. (2006). Chapter 11: Hypothalamic thyroid hormone feedback in health and disease. *Prog. Brain Res.* **153**:189–207.

Friesema, E.C., Grueters, A., Biebermann, H., Krude, H., von Moers, A., Reeser, M., Barrett, T.G., Mancilla, E.E., Svensson, J., Kester, M.H., Kuiper, G.G., Balkassmi, S., Uitterlinden, A.G., Koehrle, J., Rodien, P., Halestrap, A.P., and Visser, T.J. (2004). Association between mutations in a thyroid hormone transporter and severe X-linked psychomotor retardation. *Lancet* **364**:1435–1437.

Friesema, E.C., Jansen, J., Milici, C., and Visser, T.J. (2005). Thyroid hormone transporters. *Vitam. Horm.* **70**:137–167.

Friesema, E.C., Kuiper, G.G., Jansen, J., Visser, T.J., and Kester, M.H. (2006). Thyroid hormone transport by the human monocarboxylate transporter 8 and its rate-limiting role in intracellular metabolism. *Mol. Endocrinol.* (electronic publication August 3, preprint).

Gaitan, E., ed. (1989). *Environmental Goitrogenesis*. CRC Press, Boca Raton, FL.

Greer, M.A., Goodman, G., Pleus, R.C., and Greer, S.E. (2002) Health effects assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodine uptake in humans. *Environ. Health Perspect.* **110**:927–937.

Greer, M.A., Sato, N., Wang, X., Greer, S.E., and McAdams, S. (1993). Evidence that the major physiological role of TRH in the hypothalamic paraventricular nuclei may be to regulate the set-point for thyroid hormone negative feedback on the pituitary thyrotroph. *Neuroendocrinology* **57**:569–575.

Hansen, P.S., Brix, T.H., Sorensen, T.I., Kyvik, K.O., and Hegedus, L. (2004). Major genetic influence on the regulation of the pituitary-thyroid axis: A study of healthy Danish twins. *J. Clin. Endocrinol. Metab.* **89**:1181–1187.

Heyland, A., Reitzel, A.M., and Hodin, J. (2004). Thyroid hormones determine developmental mode in sand dollars (Echinodermata: Echinoidea). *Evol. Dev.* **6**:382–392.

Heyland, A., and Moroz, L.L. (2005). Cross-kingdom hormonal signaling: An insight from thyroid hormone functions in marine larvae. *J. Exp. Biol.* **208**:4355–4361.

Kato, Y., Ikushiro, S., Haraguchi, K., Yamazaki, T., Ito, Y., Suzuki, H., Kimura, R., Yamada, S., Inoue, T., and Degawa, M. (2004). A possible mechanism for decrease in serum thyroxine level by polychlorinated biphenyls in Wistar and Gunn rats. *Toxicol. Sci.* **81**:309–315.

Lechan, R.M., and Fekete, C. (2004). Feedback regulation of thyrotropin-releasing hormone (TRH): Mechanisms for the nonthyroidal illness syndrome. *J. Endocrinol. Invest.* **27**:105–119.

Lechan, R.M., and Fekete, C. (2006). Chapter 12: The TRH neuron: A hypothalamic integrator of energy metabolism. *Prog. Brain Res.* **153C**:209–235.

Liu, J., Liu, Y., Barter, R.A., and Klaassen, C.D. (1995). Alteration of thyroid homeostasis by UDP-glucuronosyltransferase inducers in rats: A dose-response study. *J. Pharmacol. Exp. Ther.* **273**:977–985.

Marchesini, G.R., Meulenberg, E., Haasnoot, W., Mizuguchi, M., and Irth, H. (2006). Biosensor recognition of thyroid-disrupting chemicals using transport proteins. *Anal. Chem.* **78**:1107–1114.

McNabb, F.M. (2006). Avian thyroid development and adaptive plasticity. *Gen. Comp. Endocrinol.* **147**:93–101.

Mendelson, J.R. III, Lips, K.R., Gagliardo, R.W., Rabb, G.B., Collins, J.P., Diffendorfer, J.E., Daszak, P., Ibanez, D.R., Zippel, K.C., Lawson, D.P., Wright, K.M., Stuart, S.N., Gascon, C., da Silva, H.R., Burrowes, P.A., Joglar, R.L., La Marca, E., Lotters, S., du Preez, L.H., Weldon, C., Hyatt, A., Rodriguez-Mahecha, J.V., Hunt, S., Robertson, H., Lock, B., Raxworthy, C.J., Frost, D.R., Lacy, R.C., Alford, R.A., Campbell, J.A., Parra-Olea, G., Bolanos, F., Domingo, J.J., Halliday, T., Murphy, J.B., Wake, M.H., Coloma, L.A., Kuzmin, S.L., Price, M.S., Howell, K.M., Lau, M., Pethiyagoda, R., Boone, M., Lannoo, M.J., Blaustein, A.R., Dobson, A., Griffiths, R.A., Crump, M.L., Wake, D.B., and Brodie, E.D., Jr. (2006). Biodiversity. Confronting amphibian declines and extinctions. *Science* **313**:48.

Nikrodhanond, A.A., Ortiga-Carvalho, T.M., Shibusawa, N., Hashimoto, K., Liao, X.H., Refetoff, S., Yamada, M., Mori, M., and Wondisford, F.E. (2006). Dominant role of thyrotropin-releasing hormone in the hypothalamic-pituitary-thyroid axis. *J. Biol. Chem.* **281**:5000–5007.

Novinec, M., Kordis, D., Turk, V., and Lenarcic, B. (2006). Diversity and evolution of the thyroglobulin type-1 domain superfamily. *Mol. Biol. Evol.* **23**:744–755.

Oppenheimer, J.H. (1983). The nuclear receptor–triiodothyronine complex: Relationship to thyroid hormone distribution, metabolism, and biological action. In: *Molecular Basis of Thyroid Hormone Action*, J.H. Oppenheimer and H.H. Samuels, eds., pp. 1–35. Academic Press, New York.

Padgett S. (2002). Feline thyroid surgery. *Vet. Clin. North Am. Small Anim. Pract.* **32**:851–859, vi.

Panciera, D.L. (2001). Conditions associated with canine hypothyroidism. *Vet. Clin. North Am. Small Anim. Pract.* **31**:935–950.

Power, D.M., Elias, N.P., Richardson, S.J., Mendes, J., Soares, C.M., and Santos, C.R. (2000). Evolution of the thyroid hormone-binding protein, transthyretin. *Gen. Comp. Endocrinol.* **119**:241–255.

RxList. (2005). *The Top 300 Prescriptions for 2005 by Number of US Prescriptions Dispensed*. Web site maintained by RxList LLC (The Internet Drug Index), Rancho Sante Fe, CA. Original data source credited as: Verispan, VONA, Yardley, PA. http://www.rxlist.com/top200.htm, accessed 10/2006.

Schreiber, G. (2002). The evolutionary and integrative roles of transthyretin in thyroid hormone homeostasis. *J. Endocrinol.* **175**:61–73.

St Germain, D.L., and Galton, V.A. (1997). The deiodinase family of selenoproteins. *Thyroid* **7**:655–668.

Sutija, M., and Joss, J.M. (2006). Thyroid hormone deiodinases revisited: insights from lungfish: A review. *J. Comp. Physiol.* **176B**:87–92.

Tata, J.R. (2006). Amphibian metamorphosis as a model for the developmental actions of thyroid hormone. *Mol. Cell Endocrinol.* **246**:10–20.

Taurog, A. (1999). Molecular evolution of thyroid peroxidase. *Biochimie* **81**:557–562.

van Haasteren, G.A., Linkels, E., van Toor, H., Klootwijk, W., Kaptein, E., de Jong, F.H., Reymond, M.J., Visser, T.J., and de Greef, W.J. (1996). Effects of long-term food reduction on the hypothalamus-pituitary-thyroid axis in male and female rats. *J. Endocrinol.* **150**:169–178.

Watanabe, M., Houten, S.M., Mataki, C., Christoffolete, M.A., Kim, B.W., Sato, H., Messaddeq, N., Harney, J.W., Ezaki, O., Kodama, T., Schoonjans, K., Bianco, A.C., and Auwerx, J. (2006). Bile acids induce energy expenditure by promoting intracellular thyroid hormone activation. *Nature* **439**:484–489.

Wolff, J. (1998) Perchlorate and the thyroid gland. *Pharmacol. Rev.* **50**:89–105.

Yamano, K., Araki, K., Sekikawa, K., and Inui, Y. (1994). Cloning of thyroid hormone receptor genes expressed in metamorphosing flounder. *Dev. Genet.* **15**:378–382.

Zoeller, R.T. (2005). Environmental chemicals as thyroid hormone analogues: New studies indicate that thyroid hormone receptors are targets of industrial chemicals? *Mol. Cell Endocrinol.* **242**:10–15.

Zoeller, R.T., and Rovet, J. (2004). Timing of thyroid hormone action in the developing brain: Clinical observations and experimental findings. *J. Neuroendocrinol.* **16**:809–818.